Global Regulatory Policy

Merck & Co., Inc.
Two Bethesda Metro Center
Suite 700
Bethesda MD 20814
Tel 301 941 1400
Fax 301 941 1406

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 2003D-0570 – Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs

Merck & Co., Inc, is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. We believe that FDA's continued effort to provide guidance on the clinical development of health care products encourages and facilitates therapeutic advances.

MRL applauds the FDA for its proactive stance on obesity as a serious and life-threatening disease and the importance of pharmacotherapy for obesity. Obesity is a significant worldwide health problem. It is associated with an increased risk of Type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, gallstones, osteoarthritis, certain forms of cancer, and an overall reduced life expectancy. It is apparent, therefore, that, beyond the intrinsic value in achieving weight loss, improvement in co-morbid conditions is clearly important.

MRL is pleased to support the effort of the FDA by providing comments on the 1996 draft FDA "Guidance for the Clinical Evaluation of Weight-Control Drugs" as requested in the Federal Register of January 26, 2004.[1] These comments and recommendations are points to consider in the development of a new guidance for anti-obesity drugs. Moreover, MRL encourages the FDA to broaden the scope of the future guidance to provide direction for sponsors on assessment of weight loss and improvements in co-morbid conditions as well as recommendations for the treatment of Metabolic Syndrome, a recently recognized condition associated with a specific clustering of cardiovascular risk factors. The comments below are intended to clarify for sponsors the interpretation of information within the new guidance.

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69 FR 3588, January 26, 2004

GENERAL COMMENTS

The following comments are points to consider from the 1996 draft guidance that MRL recommends be retained in the new guidance document.

1. Patient population

   MRL agrees that pharmacotherapy should be considered for obese patients. The definition of obesity in the 1996 draft Guidance for Weight-Control Drugs as individuals with body mass index (BMI) $\geq$30 kg/m^2 and $\geq$27 kg/m^2 with concomitant risk factors is appropriate. This definition of obesity is consistent with the recommendation from the National Heart, Lung and Blood Institute. MRL also recommends that increased waist circumference, as a surrogate for visceral adiposity, be viewed as a concomitant risk factor given its strong correlation with metabolic abnormalities, including insulin resistance, cardiovascular disease, high blood pressure, and lipid abnormalities.

2. Duration of pivotal efficacy studies

   Merck supports the proposal that pivotal studies to demonstrate weight loss efficacy for a new drug should be 12 months. However, MRL encourages the FDA to recognize that there may be special circumstances, such as the evaluation of the effects of co-administration (see below) where shorter treatment paradigms could be considered. Sponsors should discuss such situations with the FDA early in a development program.

3. Weight-loss efficacy

   MRL concurs that one of two demonstrations of weight loss is appropriate for registration: (1) statistically significant between-group difference in proportion of 5% responders ("5% responders" are those patients who lost $\geq$5% of baseline body weight) *or* (2) statistically significant difference in mean weight loss between placebo and drug treatment.

4. Quality of life benefits

   It is generally recognized that obesity negatively impacts individuals' quality of life; therefore, validated patient-reported outcome measures of the impact of obesity and weight loss on quality of life are appropriate in clinical trials to assess the benefits of drug-induced weight loss and weight maintenance. MRL endorses the suggestion in the 1996 Guidance that favorable changes in patient-reported outcomes such as quality of life may be mentioned in labeling.

POINTS TO CONSIDER IN FUTURE GUIDANCE

TRIAL CONSIDERATIONS

1. Duration of placebo run-in duration

   The 1996 draft guidance recommends that "patients should not be placed on drug as long as weight loss continues without drug but may be randomized when weight

plateaus". As most obese patients have previously failed to lose weight (or maintain weight loss) after repeated attempts of diet/exercise intervention, MRL considers such a long placebo run-in inappropriate. Furthermore, a variable-length placebo run-in presents special challenges for trial design and data analysis. For these reasons, it is unwise to require that randomization be delayed until weight loss plateaus and is appropriate to consider a shorter, fixed duration run-in period. We propose that a placebo run-in period of 2 weeks duration is adequate.

2. Methods to assess weight maintenance

The original draft guidance suggests that maintenance of weight loss may be the principal benefit of anti-obesity therapy. Further clarification on the design of studies to demonstrate weight maintenance should be detailed in the future guidance. MRL suggests three possible treatment paradigms could be used to assess weight maintenance: (1) weight maintenance after drug-induced weight loss, (2) weight maintenance after diet-induced weight loss (e.g. 6 weeks of a very low calorie diet) *or* (3) prevention of weight gain associated with use of certain medications (e.g., sulfonylurea, anti-psychotics, anti-epileptics, corticosteroids, etc.) or therapies (e.g., smoking cessation). In the first two paradigms, it should be possible to demonstrate the efficacy of drug-treatment to reduce body weight regain (or further decrease body weight) in studies of one year duration or less. Sponsors should assess the between-group difference in proportion of patients who maintain a clinically meaningful degree of weight loss (e.g., 5% of baseline body weight). For the third paradigm, it should be possible to demonstrate efficacy by establishing a statistical difference in weight gain between the drug- and placebo-treated groups in studies lasting one year or less.

3. Methods to assess improvements in obesity associated co-morbidities

Measurement of obesity-associated co-morbidity endpoints (lipids, blood pressure, and glucose tolerance) is encouraged in the 1996 draft guidance. MRL proposes the following metrics to assess the effectiveness of weight control drugs on obesity associated co-morbidities: (1) improvements in lipids, blood pressure, and/or fasting plasma glucose *or* (2) proportion of patients with a reduction in the dose of medication(s) used to treat co-morbid condition(s) (e.g., lipid-lowering therapy, anti-hypertensive therapy, and/or glucose-lowering therapy). Effects on any of the obesity-associated co-morbidities should be described in the label without regard to multiplicity.

4. Methods to assess Metabolic Syndrome

MRL encourages the FDA to consider the inclusion of patients who meet the criteria for the Metabolic Syndrome. The National Cholesterol Education Program Adult Treatment Panel III report defined metabolic syndrome as the presence of any 3 of the following 5 risk factors: abdominal obesity, elevated triglycerides, decreased HDL, increased blood pressure, or impaired fasting glucose.

MRL suggests that a treatment-related decrease in the proportion of patients satisfying the criteria for the metabolic syndrome could be used to support an indication for *Management of Metabolic Syndrome*.

5. Life-style modification

It is appropriate to recommend life-style modification, including a modestly restricted diet and regular exercise during clinical studies. However, it should be possible to conduct studies with variations of the components of life-style modification (e.g., no caloric restriction or caloric restriction applied only to one or more macronutrient components of the diet).

6. Safety data

The 1996 draft guidance specifies that safety of weight control drugs for long-term administration must be demonstrated in 1500 subjects for 12 months and 200-500 subjects for 24 months. These numbers greatly exceed the ICH-E1A (*Guideline for Industry: The extent of population exposure to assess clinical safety*). This ICH guideline specifies that 1500 subjects should be exposed to short-term exposure to drug, 300-600 patients for 6 months and 100 patients for a minimum of 1 year. MRL proposes the updated FDA guidance for obesity should reflect the patient exposure recommendations in ICH-E1A.

7. Patient retention/missing data

MRL believes that FDA's guidance should recognize the difficulties of patient retention in obesity clinical trials. Missing data is endemic to obesity clinical trials, which makes interpreting results very difficult. MRL recommends that study reports should characterize the extent of missing data and sensitivity analyses should be performed to assess the impact of the missing data. In addition, FDA should accept the use of alternatives to carrying forward the last observation (LOCF) for the primary statistical analysis.

PROPOSED INDICATIONS TO BE INCLUDED IN FUTURE GUIDANCE

MRL suggests the following indications for weight control drugs.

1. Weight loss

The 1996 draft guidance outlines the requirements for a weight loss indication. This information should be retained in the revision.

2. Co-administration

Given the modest efficacy of the currently marketed anti-obesity therapies, there will be interest from physicians and patients to explore co-administration of existing agents with new therapies having different mechanisms of action. MRL believes that a single study is sufficient to support a co-administration indication. The study duration should be at least 6 months, unless one of the agents is indicated for short term use. Preclinical safety studies, beyond those for registration of the individual agents,

should not be necessary unless there is reason to anticipate a pharmacokinetic or pharmacodynamic interaction. In certain circumstances it may be necessary to discuss available safety data with the agency. Sponsors should be encouraged to discuss with FDA co-administration of novel therapies.

3. Weight maintenance

The existing guidance acknowledges that maintenance of prior weight loss (or prevention of weight regain) may be an important goal of drug therapy. Therefore, the future guidance should include the necessary information to enable sponsors to pursue stand-alone indications for weight maintenance and/or prevention of weight gain. MRL proposes that two independent studies (demonstrating statistically significant between-group differences) are sufficient to support registration for a stand-alone indication. Sponsors can rely on a single study for weight maintenance if it is part of a comprehensive weight loss/weight maintenance development program.

4. Improvements in associated co-morbidities

Measurement of obesity associated co-morbidities is encouraged in the 1996 draft guidance, and it is noted that improvements or worsening of any co-morbid conditions (hypertension, dyslipidemia, glucose tolerance, etc.) will be considered in the benefit vs. risk assessment of a new drug. MRL concurs that improvements in these co-morbid conditions constitute benefits of a new drug and that changes in one or more risk factors are clinically important. Furthermore, MRL considers meaningful improvements compared with placebo in one or more co-morbid conditions accompanying drug-induced weight loss an appropriate indication for the product.

5. Metabolic Syndrome

Given the association of Metabolic Syndrome with obesity, and the clear link with increased cardiovascular morbidity and mortality, MRL proposes that FDA consider an indication for this syndrome.

ADDITIONAL CONSIDERATIONS FOR FUTURE GUIDANCE

1. Abuse Liability Assessment

Many anti-obesity agents are centrally-acting anorectics which may require assessment of abuse liability potential [21CFR 314.50(c)(5)(vii)]. MRL requests that a distinction be made in the future guidance between misuse (e.g. weight loss in non-obese subjects) and abuse (e.g., unintended use of product). The absence of clear guidance for the assessment of abuse liability may hamper progress in the development of novel therapeutic agents. Therefore, MRL encourages the FDA to issue the pending guidance on Assessment of Abuse Potential of Drugs or provide specific direction to Sponsors on the preclinical/clinical studies required to assess abuse liability.

2. Biologics

   FDA should comment whether biologics will be subject to the same efficacy requirements for approval as new chemical entities. Sponsors should be encouraged to discuss with FDA on a case by case basis the safety requirements for a biological product.

3. Accelerated approval/Fast track requirements

   Obesity is now recognized in the US as a serious and life-threatening disease. MRL proposes that FDA consider weight loss drugs as eligible for accelerated approval programs including Fast Track. In addition, MRL recommends that the new guidance include specific directives on the eligibility for Fast Track review and accelerated approval for weight loss products.

We welcome the opportunity to comment on this guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

for Donald Black, MD
Vice President, Global Regulatory Policy